

## Surgical treatment of thymoma. Personal experience

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**SUMMARY:** Surgical treatment of thymoma. Personal experience.

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**Introduction.** *Thymomas (THs) are rare epithelial tumors of the thymus gland. In this study we report our personal experience in the management and surgical treatment of THs.*

**Case reports.** *We report two clinical cases treated with combined therapy (surgery followed by adjuvant therapy).*

**Results.** *Total transternal thymectomy was performed in both patients. The post-operative course was uneventful. The patients received adjuvant radiotherapy and chemotherapy. No relapse has been observed during follow-up.*

**Discussion.** *THs are usually slowly growing tumors with similar incidence in both sexes. They occur through a wide age range, with a peak in the fifth and sixth decades. Distinctive features reminiscent of the normal thymus make the pathologic diagnosis of THs easy in most cases. Malignant behaviour is indicated by microscopic or macroscopic invasion of the tumor capsule or surrounding organs or by the presence of metastases. Although there is no standardized staging system for thymoma, the one proposed by Masaoka is commonly employed. Total thymectomy is the procedure of choice, even for encapsulated tumors, with carefully exploration of the mediastinum for evidence of ectopic thymic tissue or local invasion.*

**Conclusions.** *Despite an indolent course and a cytologically bland appearance, all thymic tumors can manifest a malignant behavior. Surgery continues to be the mainstay of treatment, and the ability to achieve complete resection seems to be the most important prognostic factor. Multimodality treatment involving postoperative chemotherapy and radiotherapy appears to increase the rate of complete resection and improves survival in advanced THs.*

**RIASSUNTO:** Trattamento Chirurgico del timoma. Esperienza personale.

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**Introduzione.** *I timomi sono rari tumori del timo. Riportiamo la nostra esperienza nella gestione e nel trattamento chirurgico dei timomi.*

**Casi clinici.** *Riportiamo due dei casi clinici giunti alla nostra osservazione, trattati con terapia combinata (chirurgia e terapia adiuvante)*

**Risultati.** *In entrambi i pazienti è stata eseguita con successo una timectomia totale trans-sternale, con successiva radio-chemioterapia adiuvante. Il follow-up è negativo per entrambi i pazienti.*

**Discussione.** *I timomi sono solitamente tumori a lenta crescita, con incidenza simile in entrambi i sessi e con un picco di incidenza tra i 50 e i 60 anni. Caratteristiche distintive che ricordano il timo normale consentono di ottenere una diagnosi istologica nella maggior parte dei casi. Il comportamento maligno è indicato dall'invasione microscopica o macroscopica della capsula o di organi circostanti o dalla presenza di metastasi. Anche se non esiste un sistema standardizzato di stadiazione, quello proposto da Masaoka è quello comunemente impiegato. La timectomia totale è la procedura di scelta, anche per i tumori capsulati, con attenta esplorazione del mediastino per evidenziare la presenza di tessuto timico ectopico o di un'invasione locale.*

**Conclusioni.** *Nonostante un decorso clinico indolente e un aspetto citologicamente blando, tutti i timomi possono manifestare un comportamento maligno. La chirurgia continua ad essere il gold standard della terapia, e la radicalità chirurgica sembra essere il fattore prognostico più importante. La terapia multimodale (chemioterapia e radioterapia post-operatoria) sembra aumentare il tasso di sopravvivenza e di resecabilità nei timomi avanzati.*

**KEY WORDS:** Thymoma - Thymectomy - Clinical cases.  
Timoma - Timectomia - Casi clinici.

### Introduction

Thymomas (THs) are rare epithelial tumors of the thymus gland; recent reports found the annual incidence to be 0.15 / 100,000 / years in the United States (1) and 0.1 / 100,000 / year in Italy (2).

They are typically slow-growing tumors that spread

by local extension. Metastases are usually confined to the pleura, pericardium, or diaphragm; extrathoracic metastases are uncommon, but they have a propensity for late recurrence even after complete resection (3).

In this study we report our personal experience in the management and surgical treatment of THs.

## Case reports

### Case 1

Male, 20 yrs old, student, with 3-months of asthenia, eyelid ptosis and diplopia. The clinical and neurological diagnosis was myasthenia gravis (MG), treated with pyridostigmine bromide 240 mg/day and corticosteroids. CT showed a solid mass (6x5 cm) in the anterior superior mediastinum, poorly vascularized, with calcifications in its context and lacking of a clear cleavage plane with the innominate vein, aortic arch and left pulmonaryilus (Fig. 1A).

With the suspect of TH, the patient underwent complete median sternotomy, visualization of the thymus to evaluate its cervical and mediastinal extent, opening of both pleural spaces to identify the phrenic nerves, and blunt dissection to separate the inferior thymic horns from the precardial fat and the superior horns from the thyro-thymic ligament (Fig. 1B). No invasion of surrounding structures was identified. By using an angled clamp and blunt dissection technique, the middle portions of the left and right lobes with surrounding fatty tissues were pulled back from the area above the phrenic nerve (which on the left runs closer to the thymus than the right) up to the junction of the innominate vein and superior vena cava; so the lateral arterial supply was ligated and divided. Once all four horns were successfully mobilized, the venous drainage to the innominate vein was clamped, ligated and divided; hemostasis was performed, sternum was approximated with interrupted wires and

the soft tissues were closed with absorbable stitches; one chest tube was placed.

The patients was extubated after 48 hrs in the Intensive Care Unit and transferred to the recovery room, where the course was uneventful. Chest tube was removed when the output was low (72 hrs after) and the patient was discharged on the 6<sup>th</sup> postoperative day with medical therapy.

At histological examination the diagnosis was type B2-B3 thymoma with lymphocytes CD5+, CD2+, CD1a+ (Figs. 1C-1D). Radiotherapy (45 Gy) and chemotherapy (cisplatin) with corticosteroids were given.

Two-year follow-up is negative for relapse.

### Case 2

Male, 74 yrs old, retired (previous tin welder), with 1-year of generalized asthenia and chest pain. The clinical and neurological diagnosis was MG from positivity of acetylcholine autoantibodies and electromyographic pattern. CT showed a well-vascularized mass (7x8 cm) in the anterior superior mediastinum (Fig. 2A).

With the suspect of TH, the patient underwent median sternotomy. Multiple and strict adhesions with posterior face of the sternum, left innominate vein, pulmonary trunk and superior vena cava were bluntly dissected. Pleural spaces were opened and all the thymic horns were mobilized with vascular ligations after preservation of the vagi and phrenic nerves. Hemostasis was performed, sternum was approximated with interrupted wires and the soft tissue were closed with absorbable stitches; two chest tubes were placed (Figs. 2B,C).

The patient was transferred to the recovery room, where the course was uneventful. Chest tubes were removed when the output was low (72 hrs after) and the patient was discharged on the 8<sup>th</sup> postoperative day with medical therapy.

At histology the diagnosis was type B2 thymoma with lymphocytes CD5+, CD2+, CD99+ (Fig. 2D).

Radiotherapy (50 Gy) and chemotherapy (bleomycin, doxorubicin, cisplatin) with corticosteroids were given.

One-year follow-up is negative for relapse.

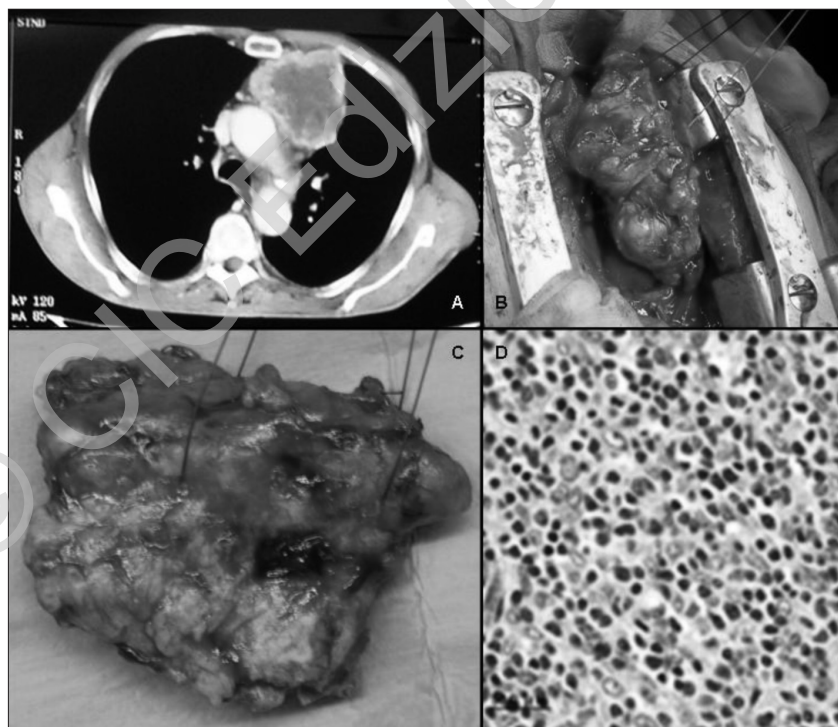


Fig. 1 - Case 1: A) CT; B) intraoperative; C) gross anatomy; D) histology.

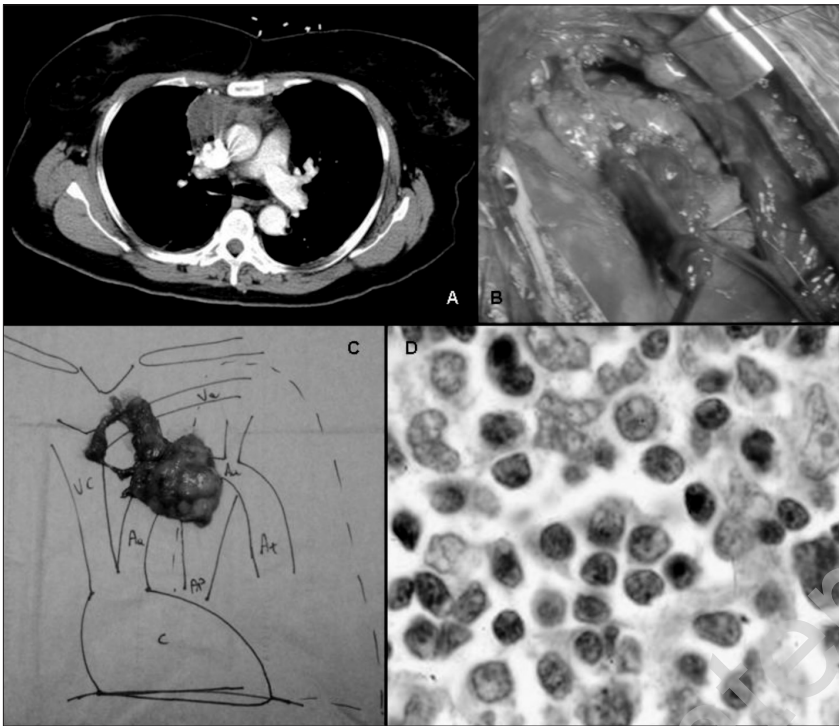


Fig. 2 - Case 2: A) CT; B) intraoperative; C) gross anatomy; D) histology.

## Discussion

THs are epithelial neoplasms arising from the thymus gland; they account for 68% of all thymic tumors and they are the most frequent neoplasms of the anterior superior mediastinum.

Typical presentation is in the 5<sup>th</sup> and 6<sup>th</sup> decades, without gender predilection. Even if TH has generally a slow-growing pattern and indolent histologic features, it can be locally invasive (30% pleura, 25% pericardium, 8% lungs, 4% recurrent laryngeal nerve) and regionally metastasizing; invasion of the heart and great vessel is extremely rare (4). Moreover, TH is associated with a number of paraneoplastic disorders: 47.7% of patients experience symptoms suggestive of MG, but other disorders such as pure red-cell aplasia (5%) and hypogammaglobulinemia (5-10%) have been described (5). About 65% of patients with MG have thymic hyperplasia, whereas only 10-15% are affected by TH (6). Approximately, 30-50% of patients are asymptomatic; 30% present with local symptoms related to the tumor encroachment on surrounding structures, such as cough, chest pain, superior vena cava syndrome, dysphagia, and hoarseness if the recurrent laryngeal nerve is involved. Finally, 30% of tumors are found incidentally on radiographic examinations during workup for MG (6).

Diagnosis of TH is usually based on radiological findings, whereas laboratory studies are not generally significant. Chest x-ray together with history and physi-

cal examination are the first step to determine the presence of the tumor, as in our experience. CT scan, dynamic Magnetic Resonance Imaging (MRI), cardiac echogram and venous angiogram are used to investigate the extent of neoplastic invasion and to improve staging and differential diagnosis determination (4). Biopsy may be useful in case of atypical presentation or if the patient is found to have an invasive tumor and is under consideration for induction therapy. The limited anterior mediastinotomy (Chamberlain approach) is the standard approach, that is typically performed over the projection of the tumor. A thoracoscopic approach for biopsy can be also used. Concern exists about the efficacy of fine-needle aspiration (FNA), that has been reported to be beneficial for diagnosis of a TH; performing a core biopsy with FNA may increase the accuracy in differentiating THs from other neoplasms, such as lymphomas and germ cell tumors (7).

The 1999 WHO histopathologic classification divided THs into 6 types and, successively, Suster and Moran proposed a simplified classification into 3 groups; the two systems are compared in Table 1 (7, 8). According to the WHO classification, the 10-year disease-free survival rate is respectively 100% for types A and AB, 83% for types B1 and B2, 35% for type B3 and 28% for type C (7). In addition, the Masaoka staging system has been developed (Table 2) (9).

Management of THs depends upon the clinical stage. Surgery is the mainstay of treatment, since most of

TABLE 1 - COMPARISON OF WORLD HEALTH ORGANIZATION SCHEMA AND THE SUSTER AND MORAN HISTOLOGICAL CLASSIFICATION OF THYMOMA.

WHO 1999	Suster and Moran 1999
<b>Type A</b> (7% of all THs); composed of a neoplastic thymic epithelial cells having spindle/oval shape, lacking nuclear atypia, and accompanied by few or no nonneoplastic lymphocytes.	<b>Thymoma</b> (well differentiated), with preservation of organotypical features of thymic differentiation; no cytological evidence of atypia.
<b>Type AB or Mixed</b> (28% of all THs); foci with features of type A thymoma admixed with foci rich in lymphocytes.	<b>Thymoma</b> (well differentiated), with preservation of organotypical features of thymic differentiation; no cytological evidence of atypia.
<b>Type B1</b> (16% of all THs); resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla.	<b>Thymoma</b> (well differentiated), with preservation of organotypical features of thymic differentiation; no cytological evidence of atypia.
<b>Type B2</b> (18% of all THs); a tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes. Perivascular spaces are common and sometimes very prominent. A perivascular arrangement of tumor cells resulting in a palisading effect may be seen.	<b>Thymoma</b> (well differentiated), with preservation of organotypical features of thymic differentiation; no cytological evidence of atypia.
<b>Type B3</b> (28% of all THs); predominantly composed of epithelial cells having a round or polygonal shape and exhibiting no or mild atypia. They are admixed with a minor component of lymphocytes, resulting in a sheetlike growth of the neoplastic epithelial cells.	<b>Atypical thymoma</b> (moderately differentiated) with partial preservation of organotypical features of differentiation and mild to moderate cytological atypia.
<b>Type C</b> (3% of all THs); clear-cut cytologic atypia and a set of cytoarchitectural features no longer specific to the thymus, but rather analogous to those seen in carcinomas of other organs. Lack immature lymphocytes; whatever lymphocytes may be present are mature and usually admixed with plasma cells.	<b>Thymic carcinoma</b> (poorly differentiated), with loss of organotypical features of differentiation; presence of overt cytological evidence of malignancy.

TABLE 2 - MASAOKA STAGING OF CLINICAL STAGES OF THYMOMA AND RELATED TREATMENT.

STAGING	TREATMENT
<b>STAGE I</b> - Encapsulated tumor with no gross or microscopic invasion	Complete surgical excision
<b>STAGE II</b> II A - Encapsulated tumor with microscopic invasion of the capsule II B - Macroscopic invasion into the mediastinal fat or pleura or microscopic invasion into the capsule;	Complete surgical excision and postoperative radiotherapy to decrease the incidence of local recurrence
<b>STAGE III</b> - Invasion of the pericardium, great vessels, or lung	Complete surgical excision and postoperative radiotherapy to decrease the incidence of local recurrence
<b>STAGE IV</b> IV A - Pleural or pericardial metastatic spread IV B - Systemic lymphatic or hematogenous metastatic spread	Surgical debulking, radiotherapy, and chemotherapy

these tumors are localized. Several large studies (>100 patients) demonstrated that complete resection is an independent prognostic factor on multivariate analysis for both localized and locally invasive THs; radiation therapy and chemotherapy have been also applied widely as adjuvant and palliative procedures (10). From relevant literature data, the resectability rates for stages I, II, III, and IV were respectively 100%, 43%-100%, 0-85%, and

0-42% (10). Kondo and Monden reported the therapeutic modalities of 1,320 patients: most patients with stage I TH underwent only surgery; about 50% of the patients with stage II and 75% of the patients with stage III underwent surgery with adjuvant therapy; most adjuvant therapies in stages I, II, and III TH consisted of radiotherapies because THs are moderately radio-sensitive; 70% of the patients with stage IV TH un-

derwent surgery with adjuvant therapy and in more than 50%, adjuvant therapy included chemotherapy (PAC: cisplatin, doxorubicin and cyclophosphamide or cisplatin and etoposide plus steroid therapy or ADOC: cisplatin, epirubicin and etoposide) (11).

The role of thymectomy is based on the evidence that “the less thymus left behind, the better the results”. Several surgical options have been proposed, with variable extent of resection: “combined transcervical-transsternal thymectomy” (T4), which allows total exposure of the district with extensive neck and mediastinum dissection (98-100% estimated range of extent of resection), but carries a high risk for nerve injury; “extended transsternal thymectomy” (T-3b), with estimated range of extent of resection 85-95%; “classic VATS thymectomy” (T-2a), with unilateral approach (80-85% estimated range of extent of resection); “video-assisted thoracoscopic extended thymectomy” (VATET) (T-2b), with bilateral visualization of the mediastinum (85-90% estimated range of extent of resection); “extended transcervical thymectomy” (T-1b), with 75-80% estimated range of extent of resection. The “basic transcervical thymectomy” (T-1a) and the “standard transsternal thymectomy” (T-3a) are actually considered incomplete, because the estimated range of extent of resection is respectively 40-50% and 70-80% (12, 13) (Figs. 3, 4). The reported cumulative operative mortality is 2.5% (range 0.7%-4.9%) (9).

From a Canadian review on 2,734 THs published after the development of Masaoka staging system, for stage I, the 5-year survival ranged from 89% to 100% and the 10-year survival ranged from 87% to 100%. For stage II, the 5-year survival ranged from 71% to 95% and the 10-year survival ranged from 60% to 100%. For stage III, the 5-year survival ranged from 59% to 75% and the 10-year survival ranged from 47% to 88%. For stage IVA, the 5-year survival ranged from 34% to 71% and the 10-year survival ranged from 30% to 40%. For stage IVB, only two studies reported the 5-year survival, and this ranged from 0% to 53% (3). Complete resection was a statistically significant predictor for 5-year survival in stages I, II, and III. Several authors described resection of the pleura, lung, pericardium, and venous structures to achieve complete tumor removal. In only two studies, the extent of resection was not a predictor for overall survival (3).

THs are sensitive to chemotherapy, with an objective response in about 67% to 100% of patients, and complete response in about 7% to 57%. Cisplatin/doxorubicin-based combination regimens seem to produce the best overall response and survival rates (14).

Multimodal approach with neoadjuvant chemotherapy, surgery and postoperative radiation therapy may improve the outcome in patients with advanced THs (15).

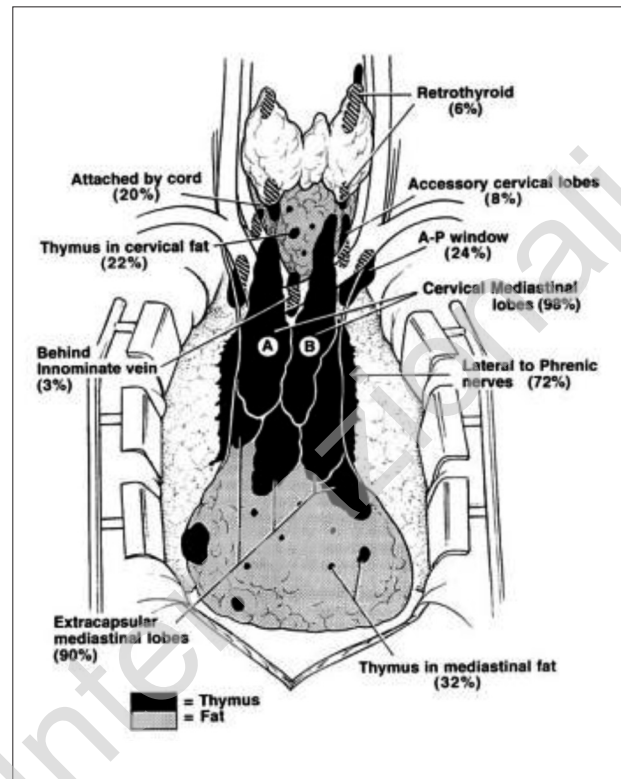


Fig. 3 - Anatomy of the thymus. The frequency of anatomic variations are noted. Black: thymus; Gray: fat. Modified from: Neurology 1997;48(Suppl 5):S52-S63.

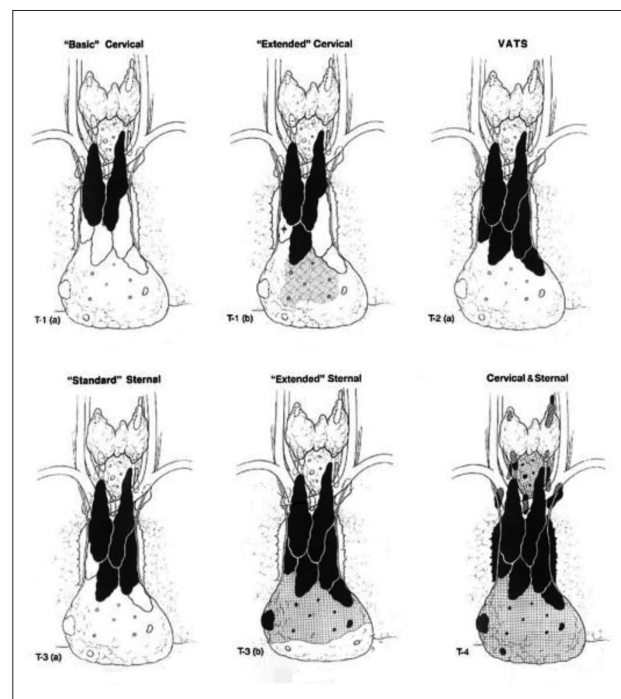


Fig. 4 - Extent of resection in thymectomy. Black: thymus; Gray: fat. Modified from: Neurology 1997;48(Suppl 5):S52-S63.

## Conclusions

Despite an indolent course and a cytologically bland appearance, all thymic tumors can manifest a malignant behavior. The aim of treatment of MG in TH is optimizing neuromuscular transmission (pyridostigmine bromide increases the efficacy of residual acetylcholine receptors) and modifying the natural history of the disease by immunosuppressive and immunomodulating drugs, before surgical resection. Optimal management for TH should be performed according to its clinical stage. Surgery continues to be the mainstay of treatment, and the

ability to achieve complete resection appears to be the most important prognostic factor, as in our case; therefore, every effort must be made at the time of resection to achieve this goal. Surgery alone should be performed for patients with non-invasive (stage I) THs. The value of postoperative radiotherapy in completely resected stage II or III tumors is questionable, but there is a benefit of postoperative radiotherapy for patients who are incompletely resected. Multimodality therapy involving preoperative chemotherapy and postoperative radiotherapy and/or chemotherapy appears to increase the rate of complete resection and improve survival in advanced (stage III and IV) THs.

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